PATENT COOPERATION TREATY

MODTAGET
02 FEB. 2005

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

ZEALAND PHARMA A/S
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DANEMARK

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	31.01.2005

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
027-2003 WO1	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK 03/00651	02.10.2003	02.10.2002

Applicant
ZEALAND PHARMA A/S et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00651

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-39 as originally filed

Claims, Numbers

1-66 as originally filed

Drawings, Sheets

1-7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 027-2003 WO1	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK 03/00651	International filing date *(day/month/year)* 02.10.2003	Priority date *(day/month/year)* 02.10.2002
International Patent Classification (IPC) or both national classification and IPC C07K14/575		
Applicant ZEALAND PHARMA A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.04.2004	31.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Fausti, S Telephone No. +49 89 2399-7389

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 52-63 (with respect to industrial applicability)

   because:

   ☒ the said international application, or the said claims Nos. 52-63 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-66 (all partially, i.e. in so far as exendin-4 derivatives with modifications at position 28 are concerned) .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-66
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-66
Industrial applicability (IA)	Yes:	Claims	1-51,64-66
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

N.1 Claims 52-63 relate to methods of treatments considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

N.2 In addition, the present set of claim is not considered to meet the requirements of Unity of Invention, and only the subject-matter of the main invention identified in the claims is examined (see below).

Re Item IV

Lack of unity of invention

U. UNITY (Rule 13.1 PCT).

U.1 The present application relates to the provision of further Exendin-4 (1-39) peptide analogues with increased stability for medical uses.

U.1 The common concept, which would link the Exendin-4 derivatives of independent claim 1 and 21 together, is the fact that these peptides comprise the amino acid sequence of Exendin (1-39), wherein up to 5 residues at positions 34-38 are eventually deleted.

U.1[a] This concept cannot be considered a common inventive concept according to Rule 13.1 PCT because it is not novel over WO 01/04156 (D1). This prior art document, which also relates to the provision of Exendin-4 analogues with increased stability for medical uses, discloses peptide analogues derived from Exendin-4 (1-39) by deletion of one or more amino acid residues at positions 34-38, and/or by conjugation to a "Z" sequence of 4-20 amino acid residues (see: abstract; claims 1 and 6; paragraphs (i), 1-3, 8, 9 and 14-19 of the examples on pages 33-43).

U.1[b] Hence, a lack of unity "a posteriori" is indicated.

U.2 In the present application, the Exendin-4 (1-39) derivatives of independent claim 1 are characterized by:
- the deletion of 0-5 amino acid residues at positions 34-38, and
- at least one of the modifications at Gln-13, Met-14, Trp-25 and Asn-28.
Despite the unclear paragraph format, but according to the punctuation signs and the Applicant's opinion (informal telephone conversation of last month), the definition of claim 1 is to be interpreted as the peptide sequence Z is the only optional feature of the claimed Exendin-4 derivatives. The semicolon ";" sign breaks off the logical statement concerning the optional features, and the following "and" conjunction introduces at least one of the residue modifications of points (i)-(iv) as an additional essential feature.

U.3 Having regards to the prior art and the different residue modifications mentioned above, there is no single technical relationship among the claimed Exendin-4 derivatives involving one or more of the technical features, to which an inventive step could be addressed (Rule 13.2 PCT). Accordingly, each of the different residue modifications relates to a separate invention or group of inventions.

U.4 The separate inventions or group of inventions are:

U.4[a] Subject 1: claims 1-66 (all partially).
Exendin-4 (1-39) derivatives comprising the modification of the residue at position 28 as defined in claims 1 or 21, compositions and medical uses thereof, methods for their preparation. The claims are partially to be considered within this group in so far as this modification is concerned.

U.4[b] Subject 2: claims 1-66 (all partially).
Exendin-4 (1-39) derivatives comprising the modification of the residue at position 14 as defined in claims 1 or 21, compositions and medical uses thereof, methods for their preparation. The claims are partially to be considered within this group in so far as this modification is concerned.

U.4[c] Subject 3: claims 1-66 (all partially).
Exendin-4 (1-39) derivatives comprising the modification of the residue at position 25 as defined in claims 1 or 21, compositions and medical uses thereof, methods for their preparation. The claims are partially to be considered within this group in so far as this modification is concerned.

U.4[d] Subject 4: claims 1-66 (all partially).
Exendin-4 (1-39) derivatives comprising the modification of the residue at position 13 as defined in claims 1 or 21, compositions and medical uses thereof, methods for their preparation. The claims are partially to be considered within this group in so far as this modification is concerned.

U.5 As no additional examination fee has been paid and the Applicant/Representative has not indicated otherwise, the examination is carried out only on the main invention, which is represented by Subject 1 as defined above.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. DOCUMENTS.

Reference is made to the following documents:

D1: WO 01/04156 A;
D2: DE 196 37 230 A;
D3: WO 00/66629 A;
D4: WO 99/43708 A.

1.1 D1 discloses peptides derived from Exendin-4 (1-39) by means of:
- the deletion of one or more amino acid residues at positions 34-38,
- the modification of Lys-40 with a lipophilic substituent, and/or
- the conjugation of the Exendin-4 peptide to a "Z" sequence of 4-20 amino acid residues (see: abstract; claims 1, 3, 6, 10 and 29-33; paragraphs (i), 1-3, 8, 9 and 14-19 of the examples on pages 33-43).

1.1[a] These Exendin-4 peptide derivatives have improved stability and are useful for the treatment of diseases associated with elevated blood glucose levels (see the abstract and claims 2, 40-48).

1.2 D2 discloses Exendin-4 peptide fragments for the treatment of diabetes (see: abstract; page 2, lines 59-63; paragraph joining pages 3 and 4). These peptide fragments can be easily synthetised in view of their short amino acid sequences (see page 4, lines 25-26).

1.3 D3 and D4 disclose Exendin derivatives with improved pharmacodynamic properties for the treatment of diseases associated with elevated blood glucose levels (see: D4, page 32, first and third paragraphs; D5, abstract and paragraph joining pages 9 and 10). In particular, these Exendin derivatives consists of an Exendin amino acid sequence linked to lipophilic groups or polyethylene glycol polymers (see: D4, claims 47 and 82-85; D5, abstract and figures 1-4J).

2. CLARITY (Art. 6 PCT).

2.1 The paragraph format used in claim 1 renders the claim definition unclear with respect to the features, which are to be considered optional. In particular, the way claim 1 is formatted is inconsistent with the punctuation signs (see the semicolon ";"), and this inconsistency leads to the lack of clarity.

2.1[a] According to the Applicant's opinion, the definition of claim 1 is to be interpreted as the peptide sequence Z is the only optional feature of the claimed Exendin-4 derivatives. Indeed, the semicolon ";" sign breaks off the logical statement concerning the optional features, and the following "and" conjunction introduces at least one of the residue modifications of points (i)-(iv) as an additional essential feature.

2.2 The definitions of claims 36, 39 and 45 are unclear with respect to the fact that the step of modifying at least one residue among Gln-13, Met-14, Trp-25 and Asn-28 is an essential or an optional additional feature of the claimed method. The lack of clarity arises because the claims read "...comprising at least one of the following steps:".

2.2[a] For consistency with the interpretation of claim 1, the step of residue modification is considered an essential feature of the claimed methods for the purpose of this examination.

2.3 Although claims 1, 21, 66 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter, i.e. to Exendin-4 derivatives, and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.

2.3[a] The same observation applies to:
- claims 27 and 32, which define pharmaceutical compositions comprising the

aforementioned Exendin-4 derivatives,
- claims 36, 39, 45 and 64, which relates to methods for producing the claimed Exendin-4 derivatives, and
- the medical use claims 52-62.

2.3[b] In addition, the reference to "the stabilized Exendin (1-39) of the invention" made in claim 64 is unclear because the expression "of the invention" does not characterize the compounds in terms of their technical features, as well as a reference to the relevant compound claims.

2.4 Claim 66 attempts to define a product in terms of the process by means of which the product can be obtained. Considering the inherent features of the product (see the PCT Guidelines 5.26), such a claim is redundant with claims 1-26 because the process itself is defined by reference to the claimed compounds. Hence, claim 66 renders the whole set of claims not concise.

3. INDUSTRIAL APPLICABILITY (Art. 33(4) PCT).

3.1 For the assessment of the present claims 52-63 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3.2 Claims 1-51 and 64-65 relate to pharmaceutical compounds, the corresponding pharmaceutical compositions and methods for their preparation. Said compounds, compositions and preparation methods can be made or applied in the pharmaceutical industry, hence they are to be considered industrially applicable according to article 33(4) PCT.

4. NOVELTY (Art. 33(2) PCT) and INVENTIVE STEP (Art. 33(3) PCT).

4.1 According to the narrower claim interpretation, which considers the modification of Asn-28 essential for the definition of the invention (see points 2.1, 2.1[a] and 2.2[a] above in combination with the observation of point U.5), the claimed subject-matter is novel because the available prior art does not disclose the deletion of one or more amino acid residues at positions 34-38 in combination with the modification of residue 28 in Exendin-4 peptides (see points 1.1-1.3 above).

4.2 D1, which can be considered to represent the relevant state of the art, discloses Exendin-4 derivatives with improved pharmaceutical properties for the treatment of diseases associated with elevated blood glucose levels (see point 1.1 above). The claimed subject-matter differs from the Exendin-4 derivatives of D1 in the specific modification at Asn-28.

4.3 The problem to be solved can therefore be regarded as the provision of further Exendin-4 (1-39) peptide analogues with improved pharmaceutical properties.

4.4 The claimed subject-matter cannot be considered as involving any inventive step because it does not solve the problem over the whole claimed scope. In particular, some of the Exendin derivatives listed in the examples of the present application fall within the claim scope, but do not have improved pharmaceutical properties over the known Exendin derivatives, as they biological activity is reduced by a factor of 10 (see compounds 7 and 14 of table 1 on page 37 and figure 9).

4.5 In addition, the claimed subject-matter lacks an inventive step for the following independent reason.

4.5[a] It appears that the Asn-28 residue is not essential for the biological activity of Exendin-4 peptides, as the N28A mutant is indicated in D3 among the suitable peptides for medical application (see compound 23 of figure 4A).

4.5[b] In the light of this observation, the Asn-28 modification as defined in the claims is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed (i.e. the provision of further Exendin-4 (1-39) peptide analogues). Such a selection can only be regarded as inventive, if it presents unexpected effects or properties in relation to the other possibilities and the known Exendin-4 derivatives. No such effects or properties are indicated in the application. In particular, the application does not provide experimental data to

support the statement, according to which the claimed Exendin peptides would have better stability and storage properties.
Hence, no inventive step is present in the subject-matter of claims 1-66.